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Pneumococcal vaccination in older adults in the era of childhood vaccination: Public health insights from a Norwegian statistical prediction study

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ABSTRACT

Two different vaccines, a 23-valent polysaccharide vaccine (PPV23) and a 13-valent conjugate vaccine (PCV13), are available for prevention of invasive pneumococcal disease (IPD) in the population aged 65 years and older (65+). The IPD epidemiology in the 65+ is undergoing change due to indirect effects of childhood immunisation. Vaccine recommendations for the 65+ must take into account these trends in epidemiology. We therefore explored the preventive potential of vaccination strategies to prevent IPD in the 65+, including PPV23, PCV13 or PCV13 + PPV23 in 2014–2019. Quasi-Poisson regression models were fitted to 2004–2014 population-wide surveillance data and used to predict incidences for vaccine-type and non-vaccine type IPD. We determined the number of people needed to be vaccinated to prevent one case per season (NNV) for each strategy and estimated the public health impact on the IPD case counts from increasing the vaccine uptake to 28–45%. Our results indicate that PCV13-IPD will decrease by 71% from 58 (95% prediction interval 55–61) cases in 2014/15 to 17 (6–52) in 2018/19 and PPV23-IPD by 32% from 168 (162–175) to 115 (49–313) cases. The NNV will increase over time for all strategies because of a decreasing vaccine-type IPD incidence. In 2018/19, the PCV13-NNV will be 5.3 times higher than the PPV23-NNV. Increasing the vaccine uptake will lead to a larger public health impact for all scenarios. Combining PCV13 and PPV23 is most effective, but the additional effect of PCV13 will decrease and is only marginal in 2018/19. Our study demonstrates the importance of increasing PPV23 uptake and of developing vaccines that confer broader immunity.

1. Introduction

Streptococcus pneumoniae (pneumococci) are part of our normal nasopharyngeal flora, but can cause severe disease such as invasive pneumococcal disease (IPD; e.g. meningitis, febrile bacteraemia). Older adults aged 65 years and older (further called 65+) are among the most vulnerable population for IPD. In most Western societies, pneumococcal vaccination is therefore recommended for the 65+. In Norway, the 23-valent pneumococcal polysaccharide vaccine (PPV23) has been recommended to the 65+ since 1996, though uptake is estimated to be only about 15–30% (unpublished data NIPH). The effectiveness of PPV23 to prevent pneumococcal disease in older adults remains subject of controversy (Shapiro et al., 1991;Moberley et al., 2013;Huss et al., 2009;Jackson et al., 2003).

Recently, a 13-valent pneumococcal conjugate vaccine (PCV13) was licenced in the EU for use in all age groups (European Medicines Agency, 2013), and at present both PPV23 and PCV13 are available for prevention of IPD in the 65+. Twelve of the PCV13 serotypes are also included in PPV23. PCV13 likely provides better protection against pneumococcal disease due to different immunogenic properties (Bonten et al., 2014). PCV13 has been used in the Norwegian childhood immunisation programme since 2011. In order to make an informed choice between PPV23 and PCV13 for

Abbreviations: IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PCV13-7, six additional serotypes that are in PCV13 but not in PCV7; PPV2323, valent polysaccharide vaccine; PPV23-11, Twelve serotypes that are in PPV23 but not in PCV13; VE, vaccine effectiveness; NVT, Non-vaccine serotypes; NIPH, Norwegian Institute of Public Health; MSIS, Norwegian Surveillance System for Communicable Diseases; 95% PI, 95% Prediction intervals; NNV, Number needed to vaccinate; PHI_s, Public health impact per future season.

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the 65+ population, evaluation of the preventive potential of the vaccines is needed.

The potential of a vaccine to prevent disease depends on the incidence of disease caused by serotypes that are covered by the vaccine, the vaccine effectiveness (VE) and the vaccine uptake. Like in other settings where PCV has been implemented in childhood immunisation programmes (Lexau et al., 2005;Miller et al., 2011;Harboe et al., 2014), the epidemiology of IPD in Norway has substantially changed, both by direct protection of immunised children, and by indirect protection due to decreased transmission of vaccine serotype pneumococci to non-vaccinated age groups (Steens et al., 2013). Simultaneously, the incidence of IPD caused by non-vaccine serotypes (NVT) has slightly increased as a result of serotype replacement (Weinberger et al., 2011;Hicks et al., 2007;Miller et al., 2011;Steens et al., 2013). Further changes in the IPD epidemiology are expected for the near future, as it will take some years before the serotype distribution has stabilised after switching to PCV13 (Hanage et al., 2010). Such future changes in IPD epidemiology should be accounted for when designing vaccine recommendations.

The aim of this work was to estimate the number of IPD cases caused by vaccine serotypes and NVT among the 65+ in the near future (2014–2019) using interrupted time series analyses based on population-wide surveillance data from 2004 through mid-2014. Furthermore, we aimed to determine the number of people needed to be vaccinated (NNV; Kelly et al., 2004) with PCV13 and/or PPV23 to prevent one IPD case per season and to calculate the potential public health impact on IPD of scenarios with different levels of vaccine uptake. Although the question of which vaccine to use in older adults has been addressed by others (Jiang et al., 2012; Smith et al., 2012; Vila-Corcoles and Ochoa-Gondar, 2013; Fedson and Guppy, 2013; Jiang et al., 2014), to our knowledge this study is the first to compare different vaccine strategies by predicting the public health impact based on data obtained in the PCV13 era.

2. Methods

2.1. Data sources

In Norway, notification of IPD is mandatory for microbiological laboratories and medical doctors and it is assumed to have a high and stable coverage. We used the serotype-specific notification data from the Norwegian Surveillance System for Communicable Diseases (MSIS; Norwegian Institute of Public Health, 2011) for IPD cases with a testing date between 1 January 2004 and 30 June 2014 and aged 65+. Data were extracted on 23 July 2014. All IPD cases, defined as a case in which *S. pneumoniae* was isolated from a normally sterile site, are notifiable to MSIS. Over 98% are isolated from blood and/or CSF and more than 90% of isolates are serotyped using the Quellung reaction with serotype-specific antisera (Vestrheim et al., 2010). According to the MSIS regulations, the NIPH does not require ethical approval for the use of notified data for this type of study.

Statistics Norway provided data on the number of Norwegian inhabitants per age group at the 1st of January of each corresponding year (Statistics Norway, 2014a), as well as predicted population sizes for the future (Statistics Norway, 2014b). We used the predicted population size at median growth and used linear interpolation to determine monthly population sizes as denominator. In 2014, Norway had 5.1 million inhabitants, of which 821,558 (16%) were 65+.

2.2. Interrupted time series analyses

We categorised our data by vaccine-type using the following designation: PCV13 serotypes, serotypes that are covered by PPV23 but not by PCV13 (PPV23–12), and NVT, defined as all serotypes not covered by PCV13 or PPV23; see Table 1.

Data were aggregated by months. Overall 7% (305/4365) of isolates missed serotype information; 58% of missings occurred in 2004/2005. Imputation of missing values was performed according to the distribution of known serotypes in the respective month, the preceding and the following month. The notified monthly IPD cases Y_t were regressed using a Poisson segmented time series analysis incorporating the changes in the Norwegian childhood immunisation programme, the population size and correcting for seasonality:

$$Y_t = \exp(\log(\mathrm{Pop}_t) + \beta_0 + \beta_1 \times \mathrm{month}_t + \beta_2 \times \mathrm{month}_t^{\mathrm{PCV7}} + \beta_3 \times \mathrm{month}_t^{\mathrm{PCV13}} + \beta_{\mathrm{seasonal}_k} + \varepsilon_t) \quad (1)$$

where month_t is the number of months from the start of the study period in January 2004, and $\mathrm{month}_t^{\mathrm{PCV7}}$ and $\mathrm{month}_t^{\mathrm{PCV13}}$ are the numbers of months after the introduction of PCV7 vaccination in July 2006 and the switch to PCV13 vaccination in April 2011, respectively; before the interventions these variables are set to zero. The term β_0 is the intercept coefficient, β_1 is the initial trend, β_2 is the change in trend post introduction of PCV7 vaccination, β_3 is the change in trend post introduction of PCV13 vaccination, $\beta_{\mathrm{seasonal}k}$ is the seasonality factor variable at month $k = 1, 2..12$, and ε_t is the error. To account for changes in the population size, the Norwegian population at month t (Pop_t) was used as an offset. To account for additional variation, we included a dispersion parameter, λ, resulting in a quasi-Poisson model.

The model Eq. (1) was fitted separately to PCV13 serotypes, PPV23–12 serotypes and NVT from 2004 through June 2014 (126 months; Fig. 1). Non-significant parameters ($p \geq 0.05$) were discarded from the final models; see Table 1. Data were analysed using GLM with the MASS package in the statistical software R version 3.1.0 (Swiss Federal Institute of Technology Zurich, 2014). The fitted models were used to predict IPD case counts for the period July 2014–June 2019 (60 months).

Seasons were defined to run from July to June the following year (e.g. July 2004–June 2005). Seasonal counts were calculated by summing the respective monthly counts. The PPV23 counts were calculated by adding the predicted values of the PCV13 and PPV23–12 models. Note that our PPV23 counts therefore include the counts for PCV13 serotype 6A, which is not included in PPV23. Due to low numbers, it was not possible to model this serotype separately and had limited effect on the final model. The frequency of serotype 6A decreased from an average of 24 cases per season in 2004–2009 to 11 in 2009/10 and further to two 6A cases in 2013/14.

2.3. The prediction intervals

We determined the 95% prediction intervals (95% PI) by taking into account both the variation related to the uncertainty in the parameters (systematic part) and the uncertainty related to the future trend. First, we performed residual bootstrapping ($N = 1000$) and refitted the models to account for the systematic part of the variation. Then, for each of the 1000 samples, we introduced uncertainty in the predicted trend by adding a random component in terms of a random walk procedure (Pearson, 1905). In each time step (month), a random normally distributed number with mean zero and standard deviation 0.00137 was drawn and the cumulated values were exponentiated and added to the predicted values. This procedure was repeated 1000 times for each bootstrap sample and the 95% PI was obtained as the 2.5% and 97.5% values of the sorted counts in each season. The value of 0.00137 was chosen based on preliminary simulations and corresponded to a change of 5% in the trend of the PCV13 counts.